The King Reaction in a Series of γ- and δ-Lactones

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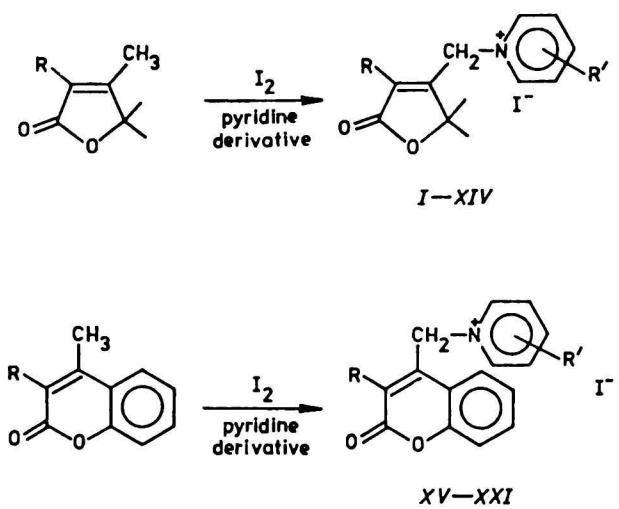
The King reaction of α,β-unsaturated γ- and δ-lactones having a reactive methyl group in position β was studied for the first time. These compounds, reacting with pyridine derivatives, afforded quaternary pyridinium salts which were tested for antimicrobial activity. An α,β-unsaturated α-cyano ester, an open-chain analogue of the above-mentioned lactones, was also used in the reaction.

Many compounds with a γ- or δ-lactone ring system are biologically active [1—3]. We decided to use the King reaction [4] for the synthesis of such lactones which would contain pyridinium, quinolinium, or isoquinolinium moieties.

It is well known that mainly acetophenones as starting compounds with a reactive methyl group have been used successfully in the King reaction. We used easily available 4,5,5-trimethyl-Δ^3-butenolides with a cyano, ethoxycarbonyl or 2-benzothiazolyl group in position 3 [5, 6] as well as 4-methylcoumarins with a cyano or 2-benzothiazolyl group in position 3 [6, 7]. The reaction proceeded by heating of equimolar amounts of a lactone and iodine in the presence of excess of a pyridine derivative in chloroform (Scheme 1). The pyridinium salts *I—XXI* with the intact lactone ring were isolated in good yields (Table 1) as intensively coloured crystalline compounds. Their IR spectra show absorption bands characteristic of the carbonyl group in α,β-unsaturated γ- and δ-lactones (at $\tilde{\nu}$ = 1710—1760 cm^{-1}), of a cyano group (2245 cm^{-1}), of the C=C bond conjugated with a carbonyl group (1610—1650 cm^{-1}), as well as of the pyridinium ring (1480—1530 cm^{-1}). ^{1}H NMR spectra contain singlets of $-CH_2-\overset{+}{N}$ group in the region of δ = 6.19—6.30.



I—XIV

XV—XXI

Scheme 1

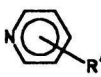
When 3-cyano-4,5,5-trimethyl-Δ^3-butenolide was heated with iodine in chloroform without a pyridine derivative, no iodomethyl derivative was formed, only starting lactone was isolated.

In our previous paper [8] we described a synthesis of 3-cyano-5,5-dimethyl-Δ^3-butenolides with a vinyl group in position 4. These compounds were intensively coloured but unstable in light. The instability can be caused, besides other factors, by low degree of substitution at the carbon atoms of the vinyl group in position 4. Now, using the King reaction, we obtained lactones with a methylene group bound with a quaternary nitrogen atom. These lactones can be used for condensation reactions with aldehydes. We expect the products of such condensations to be more stable in light because of the higher degree of substitution at the vinyl group.

Compounds *I—XXI* were tested for antimicrobial activity. However, only moderate or low activity was found, since minimum inhibitory concentrations were 50—400 μg cm^{-3} (Table 2).

Ethyl α-cyano-β-methylcinnamate can be regarded as an open-chain analogue of α,β-unsaturated α-cyano-β-methyl lactones. The cinnamate reacted with iodine and pyridine derivatives but the products did not show any characteristic bands

Table 1. Characterization of the Compounds *I*—*XXV*

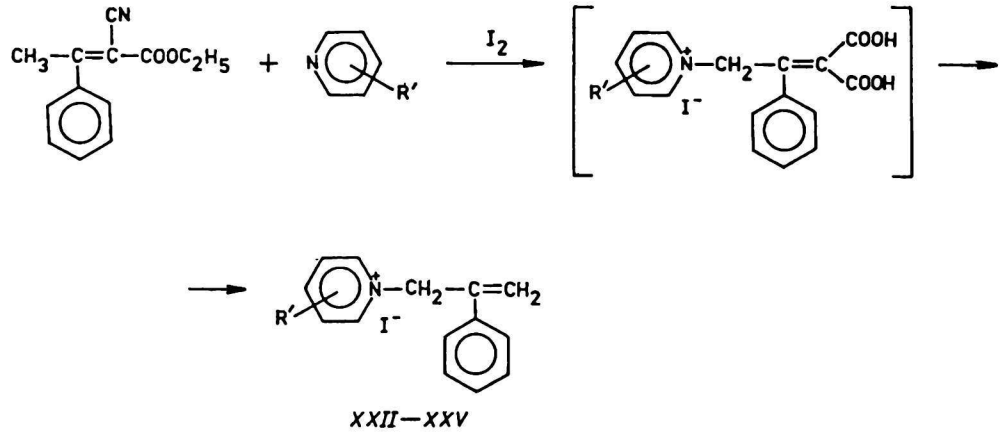
Compound	R		Formula	M_r	w_i(calc.)/% / w_i(found)/%					Yield	M.p.
					C	H	N	I	S	%	°C
I	CN	Pyridine	$C_{13}H_{13}N_2O_2I$	356.20	43.83	3.69	7.87	35.63		86	240
					43.59	3.89	8.02	35.79			
II	CN	2-Picoline	$C_{14}H_{15}N_2O_2I$	370.23	45.42	4.09	7.57	34.28		71	88—89
					45.70	3.78	7.41	33.90			
III	CN	3-Picoline	$C_{14}H_{15}N_2O_2I$	370.23	45.42	4.09	7.57	34.28		76	210—212
					45.21	3.90	7.74	33.97			
IV	CN	4-Picoline	$C_{14}H_{15}N_2O_2I$	370.23	45.42	4.09	7.57	34.28		72	134—135
					45.19	4.22	7.31	34.55			
V	CN	Quinoline	$C_{17}H_{15}N_2O_2I$	406.26	50.26	3.73	6.90	31.24		80	102
					49.89	4.01	7.15	30.88			
VI	CN	Isoquinoline	$C_{17}H_{15}N_2O_2I$	406.26	50.26	3.73	6.90	31.24		77	168—169
					50.42	3.95	7.08	31.30			
VII	$COOC_2H_5$	Pyridine	$C_{15}H_{18}NO_4I$	403.26	44.67	4.51	3.47	31.47		69	157—159
					44.37	4.32	3.60	31.59			
VIII	$COOC_2H_5$	3-Picoline	$C_{16}H_{20}NO_4I$	417.29	46.05	4.84	3.36	30.42		67	174—177
					45.84	4.98	3.19	30.07			
IX	$COOC_2H_5$	4-Picoline	$C_{16}H_{20}NO_4I$	417.29	46.05	4.84	3.36	30.42		70	116—120
					45.72	4.70	3.30	30.70			
X	$COOC_2H_5$	Quinoline	$C_{19}H_{20}NO_4I$	453.32	50.34	4.46	3.09	28.00		73	122—125
					49.96	4.18	2.87	28.21			
XI	$COOC_2H_5$	Isoquinoline	$C_{19}H_{20}NO_4I$	453.32	50.34	4.46	3.09	28.00		76	115—117
					50.13	4.52	3.52	28.45			
XII	BT	Pyridine	$C_{19}H_{17}N_2O_2IS$	464.37	49.14	3.70	6.03	27.33	6.91	82	180—182
					49.52	3.91	5.89	27.04	7.25		
XIII	BT	3-Picoline	$C_{20}H_{19}N_2O_2IS$	478.40	50.21	4.01	5.86	26.53	6.70	69	178—180
					50.01	3.85	5.91	26.46	7.02		
XIV	BT	Quinoline	$C_{23}H_{19}N_2O_2IS$	514.43	53.70	3.73	5.45	24.67	6.23	75	108—110
					53.94	3.59	5.60	24.39	6.11		
XV	CN	Pyridine	$C_{16}H_{11}N_2O_2I$	390.21	49.25	2.85	7.18	32.53		84	208—209
					48.87	3.04	6.81	32.19			
XVI	CN	2-Picoline	$C_{17}H_{13}N_2O_2I$	404.24	50.51	3.25	6.93	31.40		74	189—192
					50.22	3.51	7.23	31.75			
XVII	CN	3-Picoline	$C_{17}H_{13}N_2O_2I$	404.24	50.51	3.25	6.93	31.40		71	155—157
					50.79	3.40	7.05	31.18			
XVIII	CN	Quinoline	$C_{20}H_{13}N_2O_2I$	440.27	54.56	2.98	6.36	28.83		68	112—113
					54.80	3.15	6.27	29.11			
XIX	CN	Isoquinoline	$C_{20}H_{13}N_2O_2I$	440.27	54.56	2.98	6.36	28.83		70	166—169
					54.32	3.22	6.50	28.95			
XX	BT	Pyridine	$C_{22}H_{15}N_2O_2IS$	498.38	53.02	3.04	5.62	25.47	6.43	84	169—170
					52.81	2.75	5.91	25.19	6.75		
XXI	BT	Quinoline	$C_{26}H_{17}N_2O_2IS$	548.44	56.94	3.13	5.11	23.14	5.85	80	104—106
					57.09	3.26	4.99	22.77	6.07		
XXII	–	Pyridine	$C_{14}H_{13}IN$	322.20	52.18	4.08	4.35	39.39		81	204—207
					51.94	4.30	4.07	38.94			
XXIII	–	4-Picoline	$C_{15}H_{15}IN$	336.23	53.58	4.51	4.17	37.75		76	90—95
					53.15	4.87	4.21	37.51			
XXIV	–	Quinoline	$C_{18}H_{15}IN$	372.26	58.07	4.07	3.76	34.09		76	81—84
					58.14	3.81	4.14	33.82			
XXV	–	Isoquinoline	$C_{18}H_{15}IN$	372.26	58.07	4.07	3.76	34.09		71	115—120
					58.39	4.52	3.59	33.74			

BT = 2-benzothiazolyl.

of C≡N or of $COOC_2H_5$ group in IR spectra. Two signals corresponding with $=CH_2$ protons in the region of $\delta = 5.54-5.79$ of ^1H NMR spectra indicate that the structure is such as shown for compounds *XXII*—*XXV* in Scheme 2. Probably, the product of the King reaction is easily hydrolyzed by water present in the used pyridine derivative and the end product is formed by decarboxylation.

EXPERIMENTAL

The lactones used as the starting compounds were prepared by the methods described in previous papers [5, 6]. Melting points of products were determined on a Kofler hot-stage, the IR spectra were recorded with a Specord IR 75 instrument and ^1H NMR spectra were measured with a



XXII—XXV

Scheme 2

BS 587 (Tesla) apparatus. Antibacterial activity (*Staphylococcus aureus* Man 29/58, *Bacillus subtilis* 18/66, *Escherichia coli* 326/71, *Pseudomonas aeruginosa*) and activity against *Candida albicans* Pn-10 were tested by the plate diffusion method using Mueller—Hint and Sabouraud agar, respectively. The tested compounds were applied to paper (Whatman No. 3) disc in concentrations 400, 200, 100, 50, and 10 μg cm^{-3}. The minimum concentrations still cause a visible and measurable zone of growth inhibition. Antifungal activity against *Microsporum gypseum* and *Trichophyton rubrum* was determined by the test-tube dilution method in Sabouraud agar. All minimum inhibitory concentrations (MIC) are given in Table 2.

Table 2. Antimicrobial Activity of the Prepared Compounds

Compound	MIC/(μg cm^{-3})						
	A	B	C	D	E	F	G
I	200	200	200	400	200	100	200
III	200	400	400	>400	200	200	200
IV	200	200	400	>400	400	200	200
V	200	200	200	400	200	100	100
VI	200	200	400	400	200	100	200
VII	200	400	>400	>400	400	200	400
VIII	200	400	>400	>400	400	200	400
IX	200	200	400	400	200	200	200
X	200	200	400	400	200	100	200
XI	100	200	200	400	200	100	200
XII	50	100	200	200	100	100	100
XIII	100	100	200	400	100	100	200
XIV	50	100	200	200	200	100	200
XV	200	400	400	>400	400	200	400
XVI	200	400	400	400	400	200	400
XVII	200	400	400	400	400	200	200
XVIII	100	100	200	400	200	100	100
XIX	200	400	400	>400	400	200	400
XX	50	100	200	400	200	100	100
XXI	50	100	200	400	200	100	200

A - *Staphylococcus aureus*; B - *Bacillus subtilis*; C - *Escherichia coli*; D - *Pseudomonas aeruginosa*; E - *Candida albicans*; F - *Microsporum gypseum*; G - *Trichophyton rubrum*.

Pyridinium Iodides *I—XXV*

A mixture of a lactone or ethyl α-cyano-β-methylcinnamate (0.01 mol), iodine (0.01 mol), pyridine derivative (10 cm^3), and chloroform (50 cm^3) was refluxed for 2 h. The mixture was then left to stand at room temperature for 24 h. The solid was filtered off and thoroughly washed with ether. The melting points, yields, and the results of elemental analysis are given in Table 1.

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